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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,116	11/20/2001	John H. Healey	9958-004-999	6037

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EXAMINER	
JAGOE, DONNA A	
ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,116	HEALEY ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-117 and 122-125* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *77-117 and 122-125* is/are allowed.

6)☒ Claim(s) *38-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/21/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The amendment filed 13 April 2005 has been received and entered. Claims 77, 89-93 and 110-116 have been amended and claims 118-121 have been canceled. New claims 122-125 have been added. Claims 38-117 and 122-125 are pending to which the following grounds of rejection are or remain applicable.

Claims 38-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anuta U.S. Patent No. 4,341,691 and Lehtinen U.S. Patent No. 5,733,564.

Lehtinen et al teach bisphosphonate added to solution used for preservation of endo-osteal materials such as artificial joints, hip prostheses, dental and other implants (column 2, lines 25-36). Lehtinen teaches that bisphosphonate's main effect is their ability to inhibit bone resorption (column 3, lines 21-23). As an example, clodronate (a bisphosphonate) is employed to treat tibias, which were then more quickly and more extensively vascularized than the control tibias. It does not teach zoledronate, pamidronate, etidronate or alendronate. It would have been made obvious to one of ordinary skill in art at the time it was made to substitute zoledronate, pamidronate, etidronate or alendronate, all bisphosphonates, for the clodronate of the prior art. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532. It does not teach particle size as recited in dependent claims 50 and 51. Anuta teaches that the poly methyl methacrylate powder in Zimmers standard bone cement is comprised of a mixture of 65

to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It would have been made obvious to one of ordinary skill in art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It does not teach the addition of bisphosphonates. It would have been obvious to employ a bisphosphonate in the bone cement motivated by the teaching of Lehtinen who teaches that bisphosphonate's main effect is their ability to inhibit bone resorption (column 3, lines 21-23). Such a modification would have been motivated by the reasoned expectation of producing a bone cement which is effective in comprehensively inhibiting bone resorption.

Claims 54-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mao et al. U.S. Patent No. 6,238,687 B1 and Gayer et al. U.S. Patent No. 6,214,049 B1.

Mao et al. teach polymeric materials that can be used to produce surgical devices such as molded appliances (column 7, lines 4-12). The polymers can be used in a composition containing an active substance and can be used to produce a bone cement for repairing injury to bone (column 21, lines 10-16). The other active agents that can be added to the bone cement are anti-neoplastics, estrogenic substances,

cholesterol-lowering agents such as cholestyramine, and gallium nitrate and titanium compounds (column 22. line 4 to column 23, line 17). It does not teach the bisphosphonates that are instantly claimed.

Gayer et al. teach moldable polymer matrix systems (column 3, lines 43-14) for bone replacement. The polymer may contain hydroxyapatite (column 10, lines 27-31) and osteoconductive factors such as bisphosphonate (column 11, lines 34-38). It does not recite the specific bisphosphonate agents instantly recited. It would have been made obvious to one of ordinary skill in art at the time it was made to substitute zoledronate, pamidronate, etidronate or alendronate for the bisphosphonate of the prior art. It is prima facie obvious to substitute equivalents, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532.

Regarding the specific concentrations recited, as anyone of ordinary skill in the art will appreciate, preferred concentrations are merely exemplary and serve as useful guideposts for the practitioner. There are, however, many reasons for varying the concentration, including by orders of magnitude; for instance, an older patient with osteoporosis or one having an unusually severe break/fracture would require a correspondingly higher concentration. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as

toxicity. For these and other self-evident reasons, it would have been obvious to have used the doses of bisphosphonate recited instantly.

Claims 54, 61 and 70, remain rejected under 35 U.S.C. 102(a) as being anticipated by Sabokbar et al. (Ann. Rheum. Dis. October 1998).

Sabokbar et al. teach a polymethylmethacrylate (PMMA) bone cement, mixed with the bisphosphonate, etidronate, to inhibit bone resorption (see abstract). Specifically, PMMA was mixed with crushed etidronate and then polymerized according to manufacturer's instructions (see Methods). The extent of resorption was significantly less in the PMMA with etidronate than in PMMA alone suggesting that incorporation of a bisphosphonate into bone cement to inhibit macrophage-osteoclast differentiation may effectively be used to control periprosthetic osteolysis (see discussion). Sabokbar et al. teach that bisphosphonates, included in bone cement may be used to prevent or to control the bone resorption seen in aseptic loosening (see discussion).

Claims 38-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anuta U.S. Patent No. 4,341,691 and Sabokbar et al.

The claims are drawn to a composition comprising a polymeric bone cement in the form of particles and an anti-resorptive agent in the form of particles wherein the anti-resorptive agent's particle-size distribution is about the same or less than that of the polymeric bone-cement component's particle size distribution with dependent claims drawn to bisphosphonates, cholesterol lowering agents, estrogen-bisphosphonate conjugates and gallium as anti-resorptive agents and particle size's of 75 to 70 % with

an average diameter of about 25 microns and about 30 to 35 % with an average diameter of about 13 to 17 microns.

Anuta teaches that the polymethylmethacrylate (PMMA) powder in Zimmers standard bone cement is comprised of a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It does not teach the addition of a bisphosphonate.

Sabokbar et al. teach PMMA cement with the bisphosphonate etidronate incorporated into the bone cement. The composition is mixed and polymerized. When crushed, the PMMA/Etidronate has a particle size of between 1 and 10 microns. Sabokbar et al. teach that the addition of bisphosphonates with PMMA bone cement can inhibit PMMA induced osteoclast generation and bone resorption and inhibit wear debris induced osteolysis and provide a therapeutic approach to prevent aseptic loosening.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63) and add the bisphosphonate powder of Sabokbar, such a modification would have been motivated by the reasoned expectation of

producing a bone cement composition which is effective in comprehensively preventing osteoclast formation and loosening of prostheses. Additionally, It is prima facie obvious to substitute equivalents, i.e. etidronate for other bisphosphonates not recited, motivated by the reasonable expectation that the respective species will behave in a comparable manner or give comparable results in comparable circumstances. *In re Ruff* 118 USPQ 343; *In re Jezel* 158 USPQ 99; the express suggestion to substitute one equivalent for another need not be present to render the substitution obvious. *In re Font*, 213 USPQ 532.

Claims 54-76 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sabokbar et al and Claims 54-76 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sabokbar et al. and Anuta as applied to claims 38-53 above, and further in view of Merck and Co, Inc. WO 96/39107.

The claims are drawn to a composition comprising a bone-cement and an anti-resorptive agent in a sufficient amount that does not compromise the cement's chemical or mechanical properties but sufficient to prevent loosening of the bone cement from living bone, dependent claims are drawn to the amount of anti-resorptive agent added to the bone cement, and an amount of anti-resorptive agent that is not toxic to osteoblast while toxic to osteoclasts. Further dependent claims are drawn to the particle size wherein 65 to 70 percent of the particles have an average diameter of about 25 diameters and 30-35 percent of the particles are about 13 to 17 microns in diameter.

Anuta teaches that the polymethylmethacrylate (PMMA) powder in Zimmer's standard bone cement is comprised of a mixture of 65 to 70% polymer beads with a

maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63). It does not teach the addition of a bisphosphonate.

Sabokbar et al. teach PMMA cement with the bisphosphonate etidronate incorporated into the bone cement. The composition is mixed and polymerized. When crushed, the PMMA/Etidronate has a particle size of between 1 and 10 microns. Sabokbar et al. teach that the addition of bisphosphonates with PMMA bone cement can inhibit PMMA induced osteoclast generation and bone resorption and inhibit wear debris induced osteolysis and provide a therapeutic approach to prevent aseptic loosening.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ the recited particle sizes motivated by the recitation of Anuta that Zimmer's standard bone cement employs a mixture of 65 to 70% polymer beads with a maximum average size of 25 microns and 30 to 35% of the beads have been milled (column 5, lines 43-47) and a bead fraction where the bead powder is sifted to a size range of 13 to 17 microns (column 6, lines 59-63) and add the bisphosphonate powder of Sabokbar, such a modification would have been motivated by the reasoned expectation of producing a bone cement composition which is effective in comprehensively preventing osteoclast formation and loosening of prostheses. It does not teach the addition of other bisphosphonates.

Merck and Co. teach the addition of further bisphosphonates to the cement. The bisphosphonate applicable in the cement includes the free acids and pharmaceutically acceptable salts and barium salts of alendronate, clodronate, tiludronate, YM 175, ibandronate, risedronate, piridronate, pamidronate or combinations thereof (see page 5). Inhibition of bone resorption is used to refer to bone loss, especially the inhibition of removal of existing bone either from the mineral phase and/or the organic matrix phase, through direct or indirect alteration of osteoclast formation or activity (see page 6). The term "cement" encompasses the mixed cement composition containing all the ingredients and components prior to, during and after complete curing (see page 7). The PMMA beads have a substantially uniform particle size of about 5 to 20 microns average diameter (page 7 last paragraph). The polymer powder part can also contain a radiopaquing agent e.g. barium sulfate (page 8, 2nd paragraph). The amount of bisphosphonate is generally from 0.005 to 10 percent of the total cement composition. It would have been made obvious to one of ordinary skill in art at the time it was made to add additional bisphosphonates as cited in Merck and Co. Such a modification would have been motivated by the reasoned expectation of producing a bone cement/bisphosphonate composition which is effective in comprehensively preventing formation of osteoclasts and loosening of prosthetic implants.

Response to Arguments

Applicant's arguments filed 13 April 2005 have been fully considered but they are not persuasive. Applicant asserts that Lehtinen teaches using a solution of a

bisphosphonate to treat endo-osteal material and one would not know whether the anti-resorptive agents added are in the form of a particles or solution. Lehtinen is cited to show that it would have been obvious to incorporate a bisphosphonate into a bone dough composition motivated by the teaching of Lehtinen who teaches that bisphosphonates inhibit bone resorption.

Applicant asserts that the claimed invention recites the anti-resorptive agents particle size distribution is about the same or less than the polymeric bone-cement components particle size distribution. Remington's Pharmaceutical Sciences, teaches that, in mixing powders, a large difference in particle size would tend to cause demixing (page 1570 1st full paragraph). Thus, when the particle sizes are similar, the powders would tend to stay mixed. It would have been made obvious to one of ordinary skill in art at the time it was made to employ similar particle sizes of different agents motivated by the teaching of Remington's Pharmaceutical Sciences that a large difference in particle size would tend to cause demixing of a composition of powders.

In response to applicant's argument that Mao et al. and Gayer et al. do not provide teaching or motivation to one skilled in the art to make applicants claimed invention, and that it does not teach the cement to prevent loosening of the bone cement from the living bone, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Applicant asserts that Mao et al. and Gayer et al alone or in combination do not teach applicant's claimed invention, which is a composition comprising a bone cement for bonding prosthetic implants to the bone of a patient for substantially the life of the patient and an antiresorptive agent to prevent loosening of the bone cement from living bone. Applicant asserts that Mao et al. and Gayer et al. do not teach polymerization. The definition of polymerization is the process of forming a polymer. To unite two or more monomers to form a polymer. Since Mao et al. and Gayer et al. are both drawn to polymer bone cements, the method of mixing monomers together to form a polymer is well known in the bone cement art. Although the word polymerization is not expressly used in the prior art, products of identical chemical composition (monomers used to form polymers) can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims (i.e. polymerization of bone cement) are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

Claim Rejections - 35 USC § 112

Rejection of claims 116 and 118 under 35 U.S.C. §112 2nd paragraph is no longer maintained in view of the amendment.

Regarding the rejection of Sabokbar et al. under 35 U.S.C. §102(a), the rejection is maintained for claims 54, 61 and 70 and withdrawn for claims 77, 78, 80, 86, 93, 98, 100 and 109 in view of the amendments. Regarding the date of the applicant's invention disclosure, MPEP § 1.131 regarding an Affidavit or declaration of prior invention states that:

> When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§ 1.42, 1.43, or 1.47, may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based. The effective date of a U.S. patent, U.S. patent application publication, or international application publication under PCT Article 21(2) is the earlier of its publication date or date that it is effective as a reference under 35 U.S.C. 102(e). Prior invention may not be established under this section in any country other than the United States, a NAFTA country, or a WTO member country.

Allowable Subject Matter

Claims 77-117 and 122-125 are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Donna Jagoe
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11/14/2005

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